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population-based study with organized PSA-screening: results of the Swiss
ERSPC (Aarau)**

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Abstract: **OBJECTIVE:** To assess the value of positive family history (FH) as a risk factor for prostate cancer (PCa) incidence and grade among men undergoing organized PSA-screening in a population-based study. **PATIENTS AND METHODS:** The study cohort comprised all attendees of the Swiss arm of the ERSPC with systematic PSA-tests every 4 years. Men reporting first-degree relative(s) diagnosed with PCa were considered to have a positive FH. Biopsy was exclusively PSA-triggered with a threshold of 3ng/ml. Primary endpoint was PCa diagnosis. Kaplan-Meier and Cox regression analyses were used. **RESULTS:** Of 4,932 attendees with a median age of 60.9 (IQR 57.6-65.1) years, 334 (6.8%) reported a positive FH. Median follow-up duration was 11.6 years (IQR 10.3-13.3). Cumulative PCa incidence was 60/334 (18%, positive FH) and 550/4,598 (12%, negative FH) (OR 1.6, 95%CI 1.2-2.2, $p=0.001$), respectively. In both groups, most PCa diagnosed had a low grade. There were no significant differences of PSA at diagnosis, biopsy Gleason score or Gleason score on pathologic specimen among men who underwent radical prostatectomy between both groups, respectively. On multivariable analysis, age (HR 1.04, 95% CI 1.02-1.06), baseline PSA (HR 1.13 95% CI 1.12-1.14), and FH (HR 1.6, CI 1.24-2.14) were independent predictors for overall PCa incidence ($p<0.0001$ each). Only baseline PSA (HR 1.14, 95%CI 1.12-1.16, $p<0.0001$) was an independent predictor of Gleason score ≥ 7 PCa on prostate biopsy. The proportion of interval PCa diagnosed in between the screening rounds was non-significantly different. **CONCLUSION:** Irrespective of the FH status, the current PSA-based screening setting detects the majority of aggressive PCa and missed only a minority of interval cancers with a 4-year screening algorithm. Our results suggest that men with a positive FH are at increased risk for low grade but not aggressive PCa. This article is protected by copyright. All rights reserved.

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Title

A Positive Family History as risk factor for Prostate Cancer in a Population-based Study with organized PSA-Screening: Results of the Swiss ERSPC (Aarau)

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Key Words: prostate cancer screening; positive family history; prostate cancer aggressiveness; prostate-specific antigen, screening intensity.

Abstract

Objective: To assess the value of positive family history (FH) as a risk factor for prostate cancer (PCa) incidence and grade among men undergoing organized PSA-screening in a population-based study.

Patients and Methods: The study cohort comprised all attendees of the Swiss arm of the ERSPC with systematic PSA-tests every 4 years. Men reporting first-degree relative(s) diagnosed with PCa were considered to have a positive FH. Biopsy was exclusively PSA-triggered with a threshold of 3ng/ml. Primary endpoint was PCa diagnosis. Kaplan-Meier and Cox regression analyses were used.

Results: Of 4,932 attendees with a median age of 60.9 (IQR 57.6-65.1) years, 334 (6.8%) reported a positive FH. Median follow-up duration was 11.6 years (IQR 10.3-13.3). Cumulative PCa incidence was 60/334 (18%, positive FH) and 550/4598 (12%, negative FH) (OR 1.6, 95%CI 1.2-2.2, $p=0.001$), respectively. In both groups, most PCa diagnosed had a low grade. There were no significant differences of PSA at diagnosis, biopsy Gleason score or Gleason score on pathologic specimen among men who underwent radical prostatectomy between both groups, respectively. On multivariable analysis, age (HR 1.04, 95% CI 1.02-1.06), baseline PSA (HR 1.13 95% CI 1.12-1.14), and FH (HR 1.6, CI 1.24-2.14) were independent predictors for overall PCa incidence ($p<0.0001$ each). Only baseline PSA (HR 1.14, 95%CI 1.12-1.16, $p<0.0001$) was an independent predictor of Gleason score ≥ 7 PCa on prostate biopsy. The proportion of interval PCa diagnosed in between the screening rounds was non-significantly different.

Conclusion: Irrespective of the FH status, the current PSA-based screening setting detects the majority of aggressive PCa and missed only a minority of interval cancers with a 4-year screening algorithm. Our results suggest that men with a positive FH are at increased risk for low grade but not aggressive PCa. For personalized PCa early detection, more details of the relative's cancer characteristics might need to be collected

27 to better estimate the cancer biology.

Introduction

With an annual incidence of 233'000 in the United States [1] and 382'000 in Europe [2] prostate cancer (PCa) presents a major health issue. Population-based screening with prostate-specific antigen (PSA) has been shown to reduce cancer-specific mortality [3]. However, the main drawback of mass screening is the high rate of overdiagnosis of approximately 50% [4]. Overdiagnosis implies that the cancer detected by screening would have never become harmful during a man`s lifetime. One reason for this is the high prevalence of undiagnosed PCa shown in autopsy studies which indicates a partly low-aggressive biology [5]. Similarly, in population-based screening studies, the majority of detected PCa have low risk feature [3] most of which harbour a negligible risk to metastasize [6]. Ideally, these low-risk PCa should remain undetected which points at the need of risk-stratified screening [7].

Current urologic guidelines consider FH a strong risk factor for PCa [8, 9]. Evidence for this comes from a large twin study, showing that a positive FH is an important risk factor for future PCa development, particularly in men who have first-degree relatives affected from PCa [10]. Several other studies have confirmed FH as a risk factor of PCa [11, 12]. However, most data on this topic were collected from population registers before or at the beginning of the PSA-screening era evaluating clinically diagnosed PCa while nowadays, opportunistic PSA-screening is increasing in Western countries [13, 14]. This in turn, has led to a shift towards more localized disease and therefore dramatically changed the face of PCa in terms of a sharp increment in incidence and stage migration over the past decades [15].

There is controversial data on whether FH has an effect on cancer aggressiveness [16]. For instance, FH was an independent predictor for biochemical relapse only in the early PSA era whereas men diagnosed later on presented with more favourable cancer

characteristics [17]. Moreover, the relative risk for men with a FH for PCa decreased throughout the pre-PSA era suggesting a stage migration [18]. We hypothesized that due to the increasing screening attitude with detection of particularly low-risk disease at an earlier stage, FH might have a reduced effect on PCa incidence. Therefore, we analysed this risk factor in our screening study with an organized screening schedule where PSA-screening and subsequent biopsy were performed exclusively upon PSA-values $\geq 3\text{ng/ml}$. We hypothesize that a positive FH is not associated with aggressive PCa due to the effect of organized PSA-screening.

Materials and Methods

This study was conducted within the European Randomized Study of Screening for Prostate Cancer (ERSPC) – Switzerland. The study protocol and the population have been described previously[19]. From September 1998 to August 2003, 10'311 Swiss men aged 55-70 years were randomized 1:1 to the screening or control group, respectively. Randomization was done after informed consent. From a total of 5129 eligible men randomized to the screening arm, 4'932 (96.2%) men underwent baseline PSA-screening and were included for further analysis. In accordance with the main protocol of the ERSPC [20] a 6 core transrectal ultrasound guided lateralized prostate biopsy (or 8 core if prostate volume was >40cc) was performed if the PSA-value was ≥ 3.0 ng/ml. Biopsy was exclusively PSA-driven as per study protocol and not performed upon positive FH. PSA-screening was continued every four years until the age of 75. In a side study, men with baseline PSA of 1-3ng/ml and free-to-total ratio $\leq 20\%$ were also offered prostate biopsy at baseline (1998-2003) [21]. We also analyzed the rate of cancers emerging clinically between the screening visits. These PCa were diagnosed outside the screening protocol either by opportunistic screening, by transurethral resection of the prostate or clinically, when the diagnosis was missed by organized PSA-screening. This type of cancer was termed "*Interval PCa*".

All prostate biopsies were externally reviewed by an experienced uro-pathologist at the University Hospital Basel, Switzerland. Through periodic linkage of all men with the cancer registries, complete information on cancer incidence was obtained until December 2012. Several committees of the ERSPC accounted for the surveillance and quality of the data such as Epidemiology Committee, Pathology Committee, PSA Committee, Quality Control Committee, Causes of Death Committee with an independent Data Monitoring Committee. The Scientific Committee had access to the data and kept overview at any time [20]. PCa

104 risk was stratified according to the D'Amico classification [22]. Aggressive PCa was
105 defined as Gleason score ≥ 7 PCa.

106

107 *Statistics*

108 Comparisons between patient characteristics for men with positive and negative FH
109 were made using the Chi square test for proportions and Mann-Whitney U-test for
110 continuous variables. Univariable and multivariable Cox regression analysis was used to
111 examine the relationship between FH and time to PCa diagnosis during follow-up, with
112 age, FH and baseline PSA-value as covariates. Kaplan-Meier curves were used to
113 estimate the cancer-free survival function.

114 The Statistical Package for Social Sciences (SPSS) version 20 (IBM Corporation, NY,
115 USA) was used. All tests were two-sided with a significance level set at 0.05. The local
116 ethical committee approved the study protocol.

117

118 *Self-reported data*

119 A standardized, non-validated questionnaire including FH on first and second
120 degree relatives affected from PCa as well as International Prostate Symptom Score
121 (IPSS) amongst other parameters was mailed up-front (prior to PSA-testing) to all
122 attendees. In addition at each screening visit, all attendees underwent a structured
123 personal interview by a trained study nurse who verified the reported data. Men who
124 reported one or more first-degree relative(s) (father or brother) diagnosed with PCa were
125 considered as having a positive FH.

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Results

Clinical characteristics of 4932 attendees at baseline

All men gave information about their relatives (response rate 100%). Overall, 334 (6.8%) reported a positive FH. Most men had their father affected, n=242 (72.5%) while n=70 (21%) had brother(s) affected from the disease (table 1). Interestingly, the baseline IPSS score was higher in men with a positive FH (median 6 [IQR 3-10] vs. 5 [3-9], $p<0.0001$) (table 2). PSA at baseline was comparable between both groups. PSA-velocity at follow-up visit after 4 years was significantly higher in men with positive FH (0.32ng/ml/year vs 0.19ng/ml/year. $p=0.05$). This significant difference disappeared during follow-up visit 8 years from baseline (0.07ng/ml/year vs 0.06ng/ml/year; $p=0.8$). When PSA converted to values ≥ 3 ng/ml, biopsy compliance was comparable between both groups (77.8% [negative FH] vs. 77.3% [positive FH], respectively).

PCa incidence and cancer characteristics among men with positive vs. negative FH

During a median follow-up duration of 11.6 years (IQR 10.3-13.3), more men with positive FH (18.0%) had been diagnosed with PCa as compared to men with negative FH (12.0%) (unadjusted OR 1.61, 95%CI 1.20-2.16; $p=0.001$). In case of PCa diagnosis, age at diagnosis and Gleason score were not significantly different between both groups (table 2 and 3).

Of 334 men with positive FH, 17 (5.1%) were found to have aggressive disease defined as a Gleason score of ≥ 7 as compared to 183 of 4598 (4.9%) men with negative FH (OR 1.30; 95%CI 0.77-2.15; $p=0.3$) (table 3). Seven (1.3%) men with negative FH were found to have metastasis at the time of diagnosis (none in the positive FH group). Three of 334

155 (0.9%) and 14 (0.3%) of 4598 died from PCa during follow-up (OR 2.97; 95% CI 0.85-
156 10.38, $p=0.07$). In case of radical prostatectomy ($n=334$), Gleason score, T-stage and
157 frequency of positive lymph nodes were not significantly different between both groups
158 (table 4).

159 Incidence of interval PCa

160 Interval PCa were diagnosed outside the screening protocol either by opportunistic
161 screening, by TUR-P or clinically, when the diagnosis was missed by organized PSA-
162 screening. During the entire follow-up period, 156 cancers (3.2%) surfaced in between the
163 screening rounds or after termination of screening due to age >75 years and were
164 therefore termed *interval cancer*. Of those, 14 (4.2%) PCa emerged among men with
165 positive FH and 142 (3.1%) among men with negative FH, respectively (OR 1.46, 95%CI
166 0.83-2.56; $p=0.2$) (table 3). Biopsy Gleason scores of interval PCa were 3+3 ($n=8$
167 [57.1%]), 3+4 ($n=5$ [35.7%]), 4+3 ($n=1$ [7.1%]), $\geq 4+4$ ($n=0$ [0%]) (positive FH) and 3+3
168 ($n=79$ [55.6%]), 3+4 ($n=31$ [21.8%]), 4+3 ($n=6$ [4.2%]) and $\geq 4+4$ ($n=24$ [16.9%]) (negative
169 FH), respectively (table 3). For 2 men, Gleason score could not be classified as diagnosis
170 was achieved by clinical symptoms and PSA >100 ng/ml.

171

172 Risk factor analysis for the incidence of PCa

173 Figures 1a and b show the cumulative incidence of overall (a) and aggressive (b)
174 PCa, respectively, stratified by FH status. In multivariable analysis age, PSA and positive
175 FH at baseline were all strong independent predictors for overall PCa detection during
176 follow-up (Table 5a; $p<0.0001$ each). However, for time to aggressive PCa, only PSA at
177 baseline ($p<0.0001$), but not FH ($p=0.2$) remained an independent predictor (Table 5b).

178

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Discussion

In the current study, men with positive FH had a higher unadjusted risk for overall PCa diagnosis as compared to men with negative FH (OR 1.61, 95%CI 1.20-2.16; $p=0.001$). The PCa detection rate among men with FH is comparable to previous reports although considerably below the calculated risk of former epidemiological studies of more than twice the risk [23]. The overall prevalence of FH of 6.8% in the Swiss cohort is in line with other series and appears to be representative [24-26]. When we adjusted for other parameters, a positive FH remained an independent predictor for overall, but not aggressive PCa. Importantly, the frequency of "interval PCa" indicating a more aggressive cancer biology was only slightly but not significantly higher in men with positive FH (4.2% vs 3.1%, OR 1.46; 95% CI 0.83-2.56, $p=0.2$ respectively). Thus, systematic PSA-screening with a 4 year algorithm seems to detect potentially aggressive PCa at an earlier stage. Without this organized screening schedule, we might expect more aggressive cases among men with positive FH as compared to negative FH as it was demonstrated in studies before the screening era [18]. However, the current screening attitude in the western world clearly drifts towards opportunistic screening with early retest intervals far below 4 years [13]. This intensive screening strategy seems to weaken the real predictive effect of a first-degree relative affected from PCa.

Meta-analysis support the fact of having a first-degree relative diagnosed with PCa to be a significant risk factor for future PCa development to the index patient [27, 28]. This effect was particularly true for (clinically diagnosed) disease before the PSA-screening era. Reported risk ratios varied from 2.5 to 3.4 times as compared to men with negative FH with a greater number of family members affected or younger age at diagnosis increasing this risk even further [12]. Basically, a positive FH seems therefore to be a key factor to identify those individuals who have inherited predisposition to PCa and the goal of FH

206 inventory is to provide enough information for a risk assessment with respect to further
207 investigations. However, the predominant part of the underlying data of those studies was
208 gathered before or at the beginning of the PSA era. Having said that, some noteworthy
209 contemporary studies have failed to reproduce the correlation between a positive FH and
210 PCa aggressiveness [29]; for instance, the Prostate Cancer Prevention Trial found PSA-
211 levels, digital-rectal examination and previous biopsy but not positive FH as significant
212 predictors for high grade disease despite a very high rate of positive FH of 17% [30].
213 However, a limitation of this study was the high rate of positive FH and the randomization
214 of men with exclusively “low-risk” baseline PSA-values less or equally to 3ng/ml which
215 does not reflect the characteristics of the general population.

216

217 With the growing frequency of opportunistic PSA-based screening worldwide [13,
218 14, 31], the PCa incidence increased rapidly and most of PCa are nowadays detected at
219 an earlier stage and lower grade [15]. Mass screening is associated with an overdiagnosis
220 rate of roughly 50% [4]. Every overdiagnosed PCa in turn induces a *switch* from negative
221 to “falsely-positive” FH in relatives, which seems to dilute the true effect of FH on the
222 biological aggressiveness of PCa. The results of the current study underline this effect.
223 Whereas in early days, the odds for PCa was 2.5 to 3-fold higher in men having a 1st
224 degree relative affected from PCa [12], it dropped to 1.6 in our trial or 1.3 in the Finnish
225 arm of the ERSPC [26]. This slightly lower RR of 1.3 as compared to the current study can
226 be explained by less intensive screening protocol in Finland as men in range 3-4 ng/ml
227 underwent prostate biopsy only if free-to-total PSA ratio was less than 16%. There are still
228 true hereditary PCa having shorter lead-time and an increased risk of developing an
229 aggressive disease [32, 33]. However, in population-based studies, this proportion
230 represents only a minority of all PCa diagnosed. Additionally, the only slightly higher
231 percentage of aggressive PCa in the current study of 5.1% (positive FH) versus

232 4.0%(negative FH) suggests that at least a part of these cancers among men with a
233 positive FH were detected in their pre-clinical development phase which is actually one of
234 the very purposes of the screening intervention.

235 While FH should still be considered as a risk factor in daily practice, the assessment
236 should become much more sophisticated and detailed (e.g. the exact origins of diagnosis,
237 that is whether prostate cancer in relatives has been detected by PSA-screening or
238 clinically; a detailed analysis of tumor characteristics; the exact age at diagnosis of the
239 first degree relative affected).

240 Obviously, PCa diagnosis raises the awareness of the disease in family members as well
241 as their GPs and thereby exposes male relatives to increased PSA testing and subsequent
242 prostate biopsy. Also, a higher socioeconomic status was shown to be associated with
243 detection of more localized but not metastatic PCa [34]. Thus, a percentage of men with a
244 positive FH diagnosed with PCa are explained by increased screening behaviour.

245

246

247 There are several limitations in our study: First, we did not have complete data on
248 tumour characteristics among affected relatives, nor had we information on the three-
249 generation pedigree for more detailed FH evaluation. Second, we collected data on FH at
250 the study entrance, but this might have changed slightly over time. Therefore, there might
251 potentially be more men with a positive FH during follow-up. However, if so, this would
252 weaken the impact of positive FH even more. Finally, we have a relatively small sample
253 size as far as aggressive PCa is considered.

254 It would be of interest to comparing those with a positive FH undergoing screening to
255 those with a positive FH not undergoing screening (the control group of ERSPC).
256 However, data on FH was not collected in the control group of our trial, so this interesting

257 question cannot be answered by the data.

258 In conclusion, although our study has confirmed FH as a risk factor for PCa
259 diagnosis, most of these men were classified as having low-risk disease in this
260 contemporary population-based screening cohort. A PSA-based screening setting detects
261 the majority of aggressive PCa and missed only a minority of interval cancers with a 4-year
262 screening algorithm. FH as a risk factor might therefore rather be used complementary to
263 risk factors such as prostate volume, baseline PSA and age. For a more personalized PCa
264 early detection, information on a positive FH might need to be performed more detailed
265 including complete information on cancer characteristics.

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Ethical standards:

The study has been approved by the appropriate ethics committee

Conflict of interest:

Maciej Kwiatkowski is member of the advisory board at Astellas and has held a lecture at Myriad Genetics.

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416 Figure 1a Kaplan Meier estimate for PCa-free survival comparing positive vs negative FH
417 Figure 1b Kaplan Meier estimate for aggressive PCa-free survival comparing positive vs
418 negative FH
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